REMARKS/ARGUMENTS

Applicants note in the Office Action on Page 2 that item number 1 indicates claims 1-3 are withdrawn from prosecution. Applicants suggest that this must be an inadvertent typographical error in the Examiner's part and kindly request clarification that claims 1-2 are withdrawn from prosecution and furthermore are canceled herein. Thus, claim 3 has been and currently is pending.

Information Disclosure Statement

Applicants thank the Examiner for noting the inadvertent omission of the date for the CB1 reference by McDonnell *et al.* Applicants submit herewith a new 1449 that provides the proper citation in the interest of having this reference appear on the front of any eventually issued patent.

Drawings

Applicants submit herewith a replacement FIG. 2 to more clearly illustrate the appropriate boxed nucleotide and amino acids, pursuant to paragraph **[0317]** in the specification. No new matter is entered herein.

Status of the Claims

- Claims 3-10, 12-14, 16-20, and 22 are currently pending.
- Claims 7-9 are allowed.
- Claims 5-6 are rejected under 35 U.S.C. §112, second paragraph.
- Claims 3, 4, 10, 12, 13, 14, 16, 17, 18, 19, and 20 are rejected under 35 U.S.C. §112, first paragraph.
- Claim 22 is rejected under 35 U.S.C. §103(a).
- Claims 11, 15, 21, and 23-63 are cancelled herein without prejudice and without acquiescence. Applicants reserve the right to pursue these claims in other prosecution.
- New claims 64-65 are added herein, having support from the specification in at

least paragraph **[0342]** and original claims 1 and 2. No new matter is entered herein.

Issues under 35 U.S.C. § 112, paragraph 1

Claims 3, 4, 10, 12, 13, 14, 16, 17, 18, 19, and 20 are rejected under 35 U.S.C. § 112, first paragraph. Although the Examiner acknowledges that the specification is enabling for methods for determining a predisposition to the development of breast cancer or invasive breast cancer, wherein the presence of an A908G mutation in the nucleic acid sequence for an estrogen receptor alpha is indicative of a predisposition to developing breast cancer or invasive breast cancer, the Examiner alleges that the same specification is not enabled for diagnosis of breast cancer or methods of classifying breast cancer in an individual. Applicants respectfully disagree and assert that the specification does enable a person of skill in the art to which it pertains to make and use the invention commensurate in scope with these claims.

The Examiner cites the factors under *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) for the arguments alleging that the rejected claims are not enabled.

State of the Art

Fuqua *et al.*, published by some of the inventors of the present application, identifies an A to G transition at nucleotide 908 of the ER alpha gene in 18 or 55 premalignant regions.

Guidance and Examples in the Specification

The Examiner states that the specification does not provide any examples that support the presence of A908G being present when breast cancer is present, and the Examiner also states that the specification does not provide any examples showing that invasive breast cancer is present when the presence of A908G occurs in a cancer cell. Applicants assert that there was sufficient guidance in the specification, combined with knowledge in the art of the skilled artisan, to make and use the invention.

On page 5 of the Office Action the Examiner states that Applicant has not provided any data or evidence that suggests that each time the A908G mutation is present the

hyperplasia or adjacent normal breast tissue develops into breast cancer or invasive breast cancer (depending on the claim). Applicants assert that they are not required to show that each and every time that the A908G mutation is present that breast cancer will develop. However, as indicated in the accompanying affidavit under 37 C.F.R. §1.132 of inventor Dr. Suzanne Fuqua, the mutation is found in 90% of tested postmenopausal patients having primary invasive breast cancer. In another study, the cancer is found in 62% of breast cancer patients (33 out of 53 individuals), regardless of the breast cancers being either node-negative or node-positive. Applicants respectfully remind the Examiner that they are not claiming that the A908G mutation identifies all breast cancers, but that when the A908G mutation is present, there is a susceptibility to the development of breast cancer in the individual and/or breast cancer of the individual is diagnosed thereof. Based on the guidance taught in the specification (such as, for example, paragraphs **[0330]** and **[0331]**), the inventors demonstrate that the A908G mutation is diagnostic for a patient developing breast cancer, and particularly invasive breast cancer.

The Examiner alleges that the claims are not enabled because the mutation is found in normal tissue, and Applicants take this opportunity to recap what the specification teaches. In Example 5 of the specification, samples were obtained from hyperplasias of the breast and assayed for the mutation, in which half had the mutation identified. The size of the study was enlarged, and the mutation was then identified in 34% of the hyperplasias examined. In Example 6, the mutation was identified as a somatic change in the breast, given that its presence was detected in tissue adjacent to the hyperplasia but not noted in distant normal epithelium in the same patients. Thus, when the Examiner refers to the specification providing numerous examples of cases where the mutation is present in non-cancer tissues, Applicants respectfully assert that the Examiner is taking this information out of context. The text of the specification within paragraph **[0319]** is as follows:

> Variant A908G ERα sequence was detected along with WT sequence in the normal adjacent DNA (N Adj.) and the typical hyperplasia (TH) DNA from this patient, but the normal distant tissue (N Dis.) displayed only WT ERα sequence. All 4 of the patients with the variant ERα sequence in their hyperplastic lesion exhibited WT sequence in their distant normal tissue. To further strengthen this observation, normal DNA was also examined by direct genomic sequencing of 80 blood samples collected from patients without breast disease. There was no

> detection of the ERα variant sequence in any of these normal samples. Therefore, the A908G ERα alteration is a somatic mutation appearing frequently in association with breast hyperplasia. Thus, just as LOH can occur in morphologically normal ductal epithelium adjacent to breast cancers (Deng et al., 1996; filed herewith in a Supplemental IDS), and may therefore demarcate a localized region predisposed to the development of breast cancer, ***in a specific embodiment a somatic mutation in ERα within a localized region of normal breast epithelium defines a region of increased risk if the mutation confers a selective advantage to these cells*** (emphasis added).

Therefore, these cells from purported "normal" tissue, do in fact demarcate a localized region having cells predisposed to becoming cancerous. If the A908G somatic mutation was unrelated to breast cancer, then it would have been identified in the normal distant tissue. In fact, the normal distant tissue (N Dis.) displayed only WT ER α sequence.

Moreover, as asserted in the accompanying affidavit of inventor Dr. Suzanne Fuqua, macroscopic techniques to obtain samples *in vivo* from the breast are likely to have contaminating wild-type cells, which does not preclude the adjacent cancerous tissue from comprising cells having the A908G mutation.

Applicants assert that even if one could argue that the specification did not provide enough working examples, Applicants submit that examples may be either "working" or "prophetic", and compliance with the requirements for enablement under 35 U.S.C. 112 does not require that an example is disclosed, or that the invention be reduced to practice prior to filing, *Gould* v. *Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987) and M.P.E.P. 2164.02. Applicants, however, strongly assert that the present Examples do comply with 35 U.S.C. §112 and the invention was reduced to practice prior to filing of the priority document.

Applicants emphasize that the rejected claims are essentially for screening/diagnosis of samples having cells with the A908G mutation of ER-α receptor for breast cancer, and there is no obligation regarding patentability for the assay to be 100% correct. However, there is in fact a very reasonable correlation between this mutation and the diagnosis of breast cancer. Certainly, if the assay only identified the mutation in 70% of women suspected of having breast cancer or invasive breast cancer, then those 70% of women would clearly be

grateful such an assay exists. It is not a function of a patent to specifically exclude possible inoperative substances. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F. 2d 1569, 1576 (Fed. Cir. 1984). Furthermore, the Federal Circuit has held that § 112 does not require that the applicant describe exactly the subject matter claimed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Moreover, it is not necessary that a patent applicant test all the embodiments of his invention. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Section 112 requires simply that the patent applicant provide a disclosure that sufficiently enables one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen*, 927 F.2d at 1213.

Level of Unpredictability and Level of Skill in the Art

The Examiner alleges that it is unpredictable to conclude that the A908G mutation will lead to the presence of breast cancer, or invasive breast cancer, because the specification allegedly does not provide evidence that the presence of the mutation will necessarily result in the development of breast cancer. Applicants strongly disagree, as they have shown, for example, in paragraphs **[0330]** and **[0331]** that the A908G mutation is diagnostic for a patient developing breast cancer, and particularly invasive breast cancer. Furthermore, ***based on teachings provided in the specification*** at least at paragraphs **[0057]-[0058]**, **[0061]-[0064]**, and **[0075]-[0076]**, the data presented in the accompanying affidavit of Dr. Suzanne Fuqua is further support that the presence of the mutation will result in the development of breast cancer. A variety of ways to detect mutations are described at least in paragraph **[0065]** of the specification and are standard in the art, so the detection means itself is neither complex nor unpredictable, either.

Nevertheless, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Furthermore, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The Examiner acknowledges on Page 6 of the Office Action that the level of skill in the art is quite high, in keeping with *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986), and Applicants note that to one of such skill there is little unpredictability to obtain a breast sample and assay it for the A908G mutation in the diagnosis of breast cancer.

The Examiner makes an inaccurate statement that many *further* experiments and hundreds of patient samples would be required to enable the invention, which is inaccurate in light of the data presented in Example 10 and the affidavit provided herewith. Even still, the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cirl 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976). It is certainly routine to biopsy a sample from a breast and identify a mutation in a known nucleic acid sequence.

All that is required is that the scope of the enablement must only bear a "reasonable correlation" to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants most certainly have provided a reasonable correlation by identifying the A908G mutation in 62% (or 90%, depending on the study) of breast cancers.

Although Applicants assert that they have provided sufficient enablement in the specification to complement the high level of skill of one in this art, Applicants note that actual reduction to practice prior to filing is not required to prove enablement. *In re Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). Furthermore, it is well-settled case law that a specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). However, Applicants assert that no undue experimentation is required to make and use the invention as claimed, given that Applicants have provided the mutation in question associated with breast cancer and teach its diagnosis by a variety of means (see at least paragraph **[0065]**).

The Examiner appears to be requiring human trials as the only sufficient support for what the Examiner perceives is enablement of the claims. This is an absolutely improper

standard. Although it is expected that, for example, pharmaceutical inventions will necessitate further research and development, clinical testing is not required to obtain a patent. *In re Brana*, 51 F.3d 1560, 1569 (Fed. Cir. 1995). Appellants are not required to perform FDA-type testing or diagnosis on humans in order to obtain a patent. The Examiner in this instance appears to be confusing the requirements under the law for obtaining a patent with the requirements for obtaining government approval for marketing drugs. *Id.* at 1568.

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans.

Id. at 1667, citing In re Krimmel, 292 F.2d 948, 952 (CCPA 1961).

Furthermore, it is not a function of a patent to specifically exclude possible inoperative substances. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F. 2d 1569, 1576 (Fed. Cir. 1984).

However, even if further experiments are necessary, a considerable amount of routine experimentation is permissible, especially where the Applicants' specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986). The Office Action asserts that such experimentation is not routine, yet that argument fails to apply a standard of reasonableness to the state of the art and the relative skill of those in the art. It is well recognized "that the skill in the art of molecular biology is quite high." Id. at 548. Furthermore, time is not a sole criterion of what constitutes undue experimentation in a particular case. Therefore, in contrast to the Examiner's assertions, the experimentation is, in fact, routine, particularly given the routine nature of obtaining a breast sample and identifying the very specific A908G mutation of the ER-α nucleic acid sequence.

In discussing claim breadth, M.P.E.P. § 2164.03 provides that:

> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required.

M.P.E.P. § 2164.03, 2100-116 (1995). Should the Examiner feel that the present invention is directed to an art where certain results may be associated with a degree of unpredictability, M.P.E.P. § 2164.03 also supports Applicants' position on enablement rather than that advanced in the Action. M.P.E.P. § 2164.03 further provides:

> It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result.
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> *Id.* (quoting *In re Dreshfield*, 45 U.S.P.Q. 36 (C.C.P.A. 1940)).

Applicants assert that they have provided ***both*** sufficient ways of detecting the A908G mutation, such as in paragraph **[0065]** of the specification and appropriate guidance enabling the invention. Although some experimentation may be involved, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The correlation between particular mutations and disease states is performed by well-known means in the art, and the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Quantity of Experimentation

Although the Examiner states that many further experiments and hundreds of patient samples would be required to enable the invention, Applicants assert that this is not correct given Example 10 and the attached affidavit, but even if this is true, time-consuming experiments are acceptable if the type of experimentation is standard in the art. An extended period of experimentation may be not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Yet further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Wands*, 858 F.2d 737, 8 USPQ2d 1404 (Fed. Cir. 1985). Given that even the Examiner acknowledges the level of the

skilled artisan as being high (Office Action, page 6), it is clear that this art typically does engage in such experimentation.

Techniques in molecular biology and protein chemistry are, and were at the time of the application, well known and understood in the art. Thus, the demonstration of how to *make* the invention (obtain a sample having an ER-α nucleic acid sequence from a breast and assaying for the A908G mutation) and *use* the invention (identifying the A908G mutation as diagnostic of breast cancer) was amply provided in the specification as filed, and certainly methodically performed thereafter by the teachings provided therein, as noted in the data provided in the accompanying affidavit of Dr. Fuqua.

Conclusion

The salient issue is that in light of the direction given by the specification to the exact mutation, methods to extract samples for testing, methods to identify the mutation, the specific working example cited in the Examples, the data provided in the accompanying affidavit of inventor Dr. Fuqua, and the advanced level of skill in the art of diagnosis through molecular biology techniques, a skilled artisan would be fully aware how to make and use the invention. Thus, Applicants respectfully request removal of this rejection under 35 U.S.C. §112, paragraph 1.

Issues under 35 U.S.C. § 103(a)

Claim 22 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Kimoto (GenBank Accession Number E13443, GI: 3252248) in view of Stratagene Catalog, 1988. Although kits having PCR primers to assist in diagnosis of a disease may be known, it is certainly not taught or suggested anywhere a specific A908G mutation in an estrogen receptor alpha nucleic acid sequence could be diagnosed by such a kit. There must be some suggestion or motivation to modify the reference to achieve Applicants' presently claimed invention, which there is not, and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Therefore, Applicants respectfully request removal of the rejection of Claim 22 under 35 U.S.C. § 103(a).

In view of the above, each of the presently pending claims in this application is

believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicants submit herewith a Petition for Extension of Time of Two Months and the requisite fee. If one or more other fees are due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02102US2 from which the undersigned is authorized to draw.

Dated: December 16, 2003

Respectfully submitted,

By Melissa L. Sistrunk

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